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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,743	03/14/2001	Peter L. Pedersen	JHU1720-1	4365

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EXAMINER	
MCGARRY, SEAN	
ART UNIT	PAPER NUMBER
1635	17

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/808,743	Applicant(s) PEDERSEN ET AL.	
	Examiner Sean R McGarry	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4,5,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of Group II in Paper No. 15, filed 5/16/03 is acknowledged. The elected invention is claims 2 and 3 with claims 1 and 6-16 being linking claims. The traversal is on the ground(s) that the hexokinases defined as Type I and II are similar and may both be inhibited by an antisense constructed to target the either Type I or Type II, for example. Applicant also argues that the search of group III would be coextensive with the search of either Groups I or II. This is not found persuasive because although the sequences may have similarities, their differences are such that one would be required to make different considerations and searches for the methods claimed. As per applicants Table I it is clearly shown that Type I and Type II hexokinases are expressed in different cell types and at different levels. This clearly shows that one in the art would clearly need to search different areas (different cancers of different tissues that may be highly glycolytic in phenotype, for example). As for the Differences in groups I and II and regard to group III is clear that one could use the antisense compounds of Group III in a materially different method such as an in situ localization assay, for example. Furthermore as applicant has argued claims 1 and 6-16 are generic claims. These generic claims link the inventions of groups I and II. Claims 1 and 6-16 link(s) inventions I and II. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 1, and 6-16. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including

all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

Claims 1-3 and 6-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of growth of AS-30D hepatoma cell line in culture via the expression of SEQ ID 1 in antisense oreintation, does not reasonably provide enablement for the full scope instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make or use the invention commensurate in scope with these claims.

The instantly claimed invention is drawn to the inhibition of tumor cell in culture or in a whole animal via the inhibition of a hexokinase a targeted antisense transcript or oligonucleotide (claims 1 and 6-16). The elected invention is drawn to inhibition via antisense targeted to a type II hexokinase including SEQ ID NO: 1. The instant invention reads on antisense-based therapy of cancer. These cancers include tumors in tissues of brain, colon, urogenital, lung, renal, prostate, pancreas, liver, esophagus, stomach, hemotopoietic, breast, thymus, testis, ovary, and uterus. The invention also includes the treatment of cancers such as low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, gastric cancer, hepatoma, colorectal cancer, colorectal adenoma, acute myelogenous leukemia, lung cancer, renal cancer, leukemia, breast cancer, endometrial cancer, bone cancer, squamous cell cancer and neuroblastoma. The breadth of cancers contemplated for treatment is indeed vast. The instant specification shows the inhibition of AS-30D hepatoma cells in culture upon their transfection with an antisense Type II hexokinase (SEQ ID NO:1) expression vector. It has been shown that expression of SEQ ID NO: 1 in antisense orientation can inhibit AS-30D cell growth. The specification fails to show how the inhibition of a Type II hexokinase that may also inhibit both a Type I and Type II hexokinase in one cell line correlates to the inhibition of tumor cell growth via the inhibition of any one particular hexokinase in other cells and further in cell of a whole animal. The instant specification indicates that it is "highly likely" that both a Type I and a Type II hexokinase are inhibited

by an antisense transcript of SEQ ID NO: 1 (see page 40). The specification therefore fails to demonstrate the inhibition of cell grow is due the the inhibition of either a Type I or Type II hexokinase alone. Applicants priority document indicates that it is only Type II and to a lesser extent Type I that are over expressed in highly glycolytic tumors. It si further indicated that the experiments, which parallel those of the instant specification were designed to inhibit both Type I and Type II hexokinase (see page 3 of the priority document, for example). The instant specification has failed to show a correlation that hexokinase overexpression, for example, is causative of the broad range of cancers instantly considered for treatment. Newgard et al (US 5,891,717) states at column 17 "[h]owever, the correlation [increases in low Km hexokinase activity correlation with cell transformation] has not been proven to exist as a cause and effect relationship." This would indicate that one in the art would be required to determine the relationship of any particular hexokinase with any particular cancer to determine its suitability as a target for the treatment of a vast array of cancers, for example. Furthermore the art of antisense-based therapy is in general an unpredictable art where the instant specification provides no specific guidance for the treatment of any specific cancer by targeting any particular hexokinase, for example. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-

antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he

relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety

of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

The instant specification fails to provide any particular target for any particular disease and further has not provided any specific guidance on how to make an antisense that would be predicable effective for treating any of the vast array of diseases instantly contemplated. One in the art would be left to determine all of these determination by engaging in undue trial and error experimentation, for example.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites the limitation "wherein said cellular proliferative disorder" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703)305-7028. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SRM
July 24, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635